

Is topical haloperidol a useful glaucoma treatment?

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SUMMARY A randomised, double blind, single dose study of topical haloperidol, a dopamine receptor blocking drug, was performed on 20 healthy volunteers. After its administration a modest reduction in intraocular pressure was recorded over the six-hour study period, but the difference was not significant at the $p < 0.05$ level. Although dopamine blocking agents are effective in reducing intraocular pressure in experimental animals, topical haloperidol appears unlikely to be clinically useful in the treatment of glaucoma.

We were stimulated to examine the effect of topical haloperidol, a dopamine receptor blocking drug, on human intraocular pressure (IOP) as a result of recent work regarding timolol's mechanism of action. Topical timolol is widely used in the treatment of glaucoma but is contraindicated in patients with cardiovascular or respiratory disease, as it may precipitate serious, occasionally fatal, side effects.¹ Timolol's major side effects are the result of beta adrenergic blockade.¹ However, there is evidence that its inhibitory effect on aqueous humour secretion may not be a result of beta adrenergic blockade²⁻⁵ but of dopamine receptor blockade.⁵⁻⁸

Timolol's action may not be mediated by beta receptors, since its binding to ocular beta receptors is short lived, though its ocular hypotensive action is long lasting.² Natural beta receptors are orientated in favour of the L-isomer, so that D-timolol has only 3% of the systemic beta blocking action of L-timolol. However, D-timolol is as effective as the L isomer in reducing intraocular pressure (IOP) when infused into the cat eye.³ In addition timolol lowers intraocular pressure (IOP) in patients with third neuron Horner's syndrome, that is, in the absence of ocular sympathetic innervation.⁴

Timolol may act in part on dopamine receptors, since it reduces the concentration of dopamine in the iris and ciliary body but leaves adrenaline, noradrenaline, and prostaglandin levels unaffected.⁵

In animal experiments studying the recovery time of the IOP after intravenous infusion of hypertonic saline, topical dopamine increased the IOP while

timolol reduced it. The effect of timolol was neutralised by simultaneous dopamine administration.⁶ In this experimental model topical haloperidol, a dopamine antagonist, reduces the IOP more profoundly and for a longer duration than timolol.^{7,8}

Since there is a need for a long acting topical ocular hypotensive agent with no beta adrenergic blocking effects, we performed a single drop, double blind study of topical haloperidol in human volunteers.

Subjects and methods

This study was approved by the Ethics Committee of St Mary's Hospital. Twenty healthy subjects volunteered, and informed consent was obtained from all.

Sterile, viscous solutions of haloperidol 0.125% or haloperidol 1.0% in water containing 0.5% or 0.7% lactic acid respectively were prepared and found to have a pH 5.5.

Intraocular pressures were measured with a Goldmann applanation tonometer which was standardised before and after each test session. The same instrument was used throughout the study. The IOPs were measured after instilling topical benoxinate and fluorescein: 10 minutes before application of topical haloperidol and at two, four, and six hours after. Eye drops were instilled independently by trained ophthalmic nurses.

The first seven subjects received haloperidol 0.125%, while all others received haloperidol 1.0%. Saline or inert vehicle was applied to the control eyes. Test eyes were randomised, and the study was performed in a double blind fashion.

Visual acuities, brachial artery blood pressure, and

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Table 1 Mean percentage intraocular pressure differences from base line pressures

Preparation	% Difference at 2 hours		% Difference at 4 hours		% Difference at 6 hours	
	Active	Placebo	Active	Placebo	Active	Placebo
1% Eye drops (13 subjects)	-9.55 (±10.01)	-3.55 (±8.12)	-9.84 (±13.08)	-4.99 (±10.57)	-6.19 (±11.77)	-8.06 (±11.44)
t Test values for paired differences	1.68		1.0		0.41	
0.125% Eye drops (7 subjects)	-15.04 (±16.53)	-3.73 (±11.22)	-1.93 (±10.63)	-5.87 (18.50)	-8.1 (±14.50)	2.72 (±10.90)
t Test values for paired differences	1.5		0.32		1.33	
Total mean % differences (20 subjects)	-11.47 (±12.52)	-3.61 (±9.02)	-8.26 (±12.70)	-5.17 (±11.70)	-6.72 (±12.16)	-5.07 (±12.04)

Results given ± one standard deviation. Results not significant at the 5% level ($t < 1.96$).

pulse rate were measured at base line and at two and six hours after topical haloperidol. A full slit-lamp examination was performed before each IOP measurement, and subjects were questioned about ocular symptoms.

Volunteers were excluded from the study if there was any known or detected ocular disease, if any topical medication was in use, or if systemic beta adrenergic or dopamine receptor blocking agents were taken.

Results

Haloperidol produced a small reduction in IOP, with a maximum reduction of 11.4% at 2 hours. The mean reduction from baseline IOP in control eyes was 3.9% at 2 hours. Thereafter the difference between test and control eyes diminished (Fig. 1). The

difference was not significant at $p < 0.05$ for the numbers tested. The ocular hypotensive effect of haloperidol was of small magnitude and short duration (Table 1).

Stinging was noted by all subjects and was of sufficient intensity to induce reflex lacrimation in most of them.

A fine punctate epithelial keratitis (PEK) developed in the lower half of both test and control eyes in 50% of subjects.¹⁰ The signs resolved within a few hours and were attributed to benoxinate induced epithelial toxicity.

However two of these 10 had PEK more marked on the test eye, and a further four subjects developed lower half PEK in the test eye only, with no signs on the control eye. Thus the haloperidol/lactic acid solution may have an element of acute epithelial toxicity which is mild and of short duration.

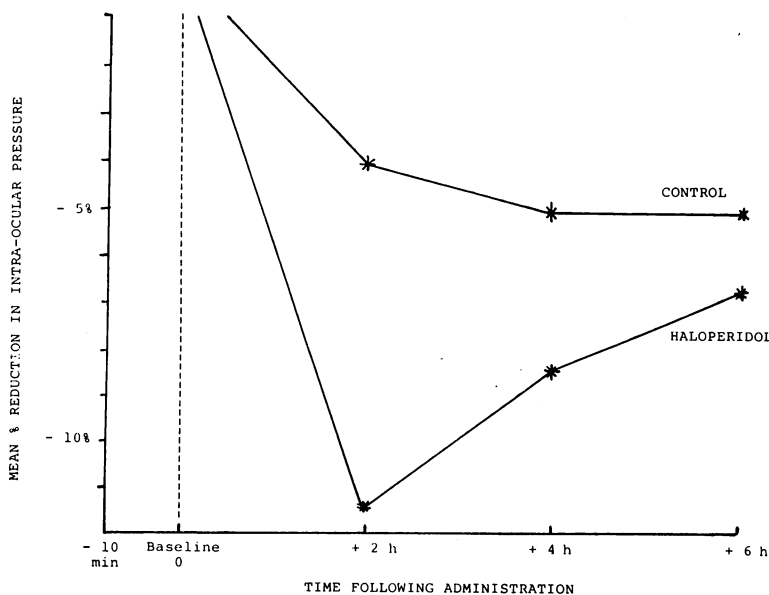


Fig. 1 Mean percentage reduction in IOP following topical haloperidol instillation.

Pupil size, visual acuity, brachial artery blood pressure, and pulse rate were unchanged over the test period.

Discussion

We wished to answer the question of whether dopamine receptor blocking drugs are effective in reducing human intraocular pressure. We chose haloperidol because it is more effective in reducing cat IOP than other dopamine blocking drugs.⁸ In addition there is long clinical experience with the use of systemic haloperidol.

Studies in experimental animals have shown an impressive ocular hypotensive effect (30% decrease in IOP) after topical haloperidol application, and it has been suggested that these drugs may be an effective treatment for glaucoma.⁸ We believe that this is the first time topical haloperidol has been tested in humans. Our results show that haloperidol produces a small reduction in IOP at 2 hours which was not statistically significant for the numbers tested. Topical haloperidol is therefore not likely to be a clinically useful agent in the treatment of patients with glaucoma.

Several factors may have contributed to the discrepancy between our results and those from animal work. In our patients haloperidol was instilled after corneal sensation had returned. Stinging was a feature of haloperidol instillation, and reflex hypersecretion may have washed the drug off the ocular surface. In a study of aqueous humour dynamics Chiou⁷ instilled haloperidol at time 0, contemporaneously with tonometry. These cats were anaesthetised with pentobarbital, and this may have prevented reflex tearing. Further, these eyes had indwelling cannulae at the time of eyedrop application, which may have artefactually increased drug penetration into the anterior chamber. Chiou's studies used the time taken to return to normal IOP after intravenous infusion of hypertonic saline as an index of rabbit aqueous humour secretion.³⁻⁶ It is possible that the mechanisms involved in the aqueous secretory response of the hyperosmolar experimental animal may differ from those maintaining physiological IOPs in humans. Finally, the question arises whether the laboratory animal and the human patient differ in their IOP pharmacology. Other workers have noted that the effect of timolol is less marked in experi-

mental animals^{2,9,10} than in humans.¹¹ This may account for the differences between haloperidol and timolol in Chiou's studies.^{7,8}

Chiou⁷ showed that haloperidol acts by increasing aqueous humour outflow and reducing aqueous humour production. Although most effective glaucoma treatments still reduce normal IOPs by 25-30%, it is possible that dopamine receptor blockers may have a greater effect in patients with glaucoma or raised IOPs. These factors may explain the discrepancies between results in human volunteers and animals.

In conclusion we find that a study of the use of haloperidol in normal human volunteers does not support a role for haloperidol as an effective glaucoma treatment. Caution is required in extrapolating results from experimental animals to humans.

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